临床研究

心脏瓣膜钙化对维持性血液透析患者心血管预后的影响

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摘要:目的 探讨心脏瓣膜钙化(HVC)对维持性血液透析(MHD)患者心血管预后的影响。**方法** 入组2009~2011年302例MHD患者(其中99例伴HVC),所有患者随访2年,采用生存曲线分析心血管终点事件,Cox回归分析心脏瓣膜钙化对心血管预后的影响。**结果** 患者初始透析的平均年龄为58.2岁,男性占53.6%。随访2年,HVC与非HVC组患者全因死亡、心血管死亡和新发心血管事件发生率分别为30.3% *vs* 16.3%、22.2% *vs* 6.9%和48.5% *vs* 25.6%(P<0.05)。生存曲线分析显示两组在全因死亡率(Log Rank P=0.006)、心血管死亡(P<0.001)和新发心血管事件(P<0.001)方面均存在统计学差异。Cox回归分析显示,校正后HVC仍然显著增加患者全因死亡[HR 1,88,95%CI:(1.11-3.19)]、心血管死亡[3.47(1.76-6.84)]和新发心血事件风险[1.64(1.09-2.47)]。**结论** HVC是MHD患者心血管死亡及新发心血管事件的独立危险因素。

关键词:心脏瓣膜钙化;血液透析;死亡;心血管事件

Association of heart valve calcification with cardiovascular outcomes in patients on maintenance hemodialysis

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Abstract: Objective To investigate the impact of heart valve calcification (HVC) on cardiovascular outcomes in patients on maintenance hemodialysis (MHD). **Methods** We enrolled 302 Chinese patients on MHD between 2009 and 2011 including 99 with HVC identified by echocardiography screening. All the patients were followed up for 2 years and survival analysis was performed with all-cause mortality, cardiovascular mortality and new onset cardiovascular events as the endpoints. Cox regression analysis was used for analyzing the impact of heart valve calcification on the cardiovascular outcomes of the patients. **Results** The mean age of the total patients was 58.2±15.0 years when receiving the initial MHD, and 53.6% were male patients. The overall mortality, cardiovascular mortality and new on-set cardiovascular events in HVC and non-HVC groups were 30.3% *vs* 16.3%, 22.2% *vs* 6.9%, and 48.5% *vs* 25.6%, respectively (P<0.05). Kaplan-Meier survival analysis showed a significant difference in all-cause mortality (P=0.006), cardiovascular mortality (P<0.001) and new-onset cardiovascular events (P<0.001) between HVC and non-HVC groups. After adjustment, Cox regression analysis identified HVC as a risk factor for increased all-cause mortality (HR=1.88; 95% CI: 1.11-3.19), cardiovascular mortality (HR=3.47, 95% CI: 1.76-6.84) and cardiovascular events (HR=1.64, 95% CI: 1.09-2.47). **Conclusions** HVC is an independent risk factor for increased cardiovascular mortality and new cardiovascular events in patients on MHD.

Key words: heart valvular calcifition; hemodialysis; mortality; cardiovascular events

透析患者被视为心血管疾病(cardiovasuclar disease, CVD)的最高危人群[1-2],其CVD死亡率比普通人群高出10~30倍[3-4],占透析患者总体死亡率的一半以上。在众多影响透析患者生存结局及CVD并发症的因素当中,血管或心脏瓣膜钙化(heart valvular calcification, HVC)是影响预后的最重要的预测标志[5-6]。

CKD患者随着肾功能的减退,钙化的罹患率逐渐增加[7]。基于一些临床证据,2009年KDIGO关于CKD-MBD(慢性肾脏病-矿物质骨病)的指南中建议,采用侧位腹部X线和心脏多普勒超声评估CKD3-5D期患者的血管及HVC情况[8]。然而,目前关于HVC对透析患者预后影响的证据并不多,主要集中在HVC对维持性血液透析(MHD)/腹膜透析(PD)患者全因预后的影响[5, 9-10],或新进入透析患者的心血管预后[11-12]。但HVC对进入维持透析的患者的心血管预后,尤其是对新发心

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血管事件的影响如何，鲜见报道。本研究旨在探讨心脏瓣膜钙化对MHD全因预后及新发心血管事件的影响。

1 对象和方法

1.1 研究对象

入组时间为2009年4月~8月，患者在广东省人民医院血液净化中心规律血液透析（透析时长≥3个月，每周2~3次，每次4 h，采用含1.25 mmol/L或1.5 mmol/L钙离子浓度、2.0~3.0 mmol/L钾离子浓度、138~140 mmol/L钠离子的碳酸氢盐透析液）的成年患者完善心脏B超筛查，根据有无心脏瓣膜钙化分成钙化组（99例）和无钙化组（203例）。患者入组时记录一般资料如年龄、性别、体质量、身高、吸烟史、开始透析时间、血管通路、超滤率及既往病史（糖尿病、高血压及心血管疾病史）等。同时评估透析充分性、血红蛋白、铁蛋白、转铁蛋白饱和度、血清白蛋白、血钙、血磷、甲状旁腺、C反应蛋白、尿酸、血清胆固醇、甘油三酯、低密度脂蛋白、高密度脂蛋白等，上述指标患者每3~6个月评估1次。统计时以患者入组时的第1次实验室检查记录为准。

1.2 心脏超声检查及心脏瓣膜钙化的定义

采用心脏彩色多普勒超声检查评估心脏瓣膜钙化的性状和程度，评估左室射血分数，分别测量各房室内径、室间隔厚度、收缩期、舒张期二、三尖瓣口血流频谱E、A峰值等。心脏瓣膜钙化定义为主动脉瓣或二尖瓣出现一个或多个环面亮回声超过1 mm[13]。

1.3 心血管事件定义及随访

心血管事件定义为脑卒中、短暂性脑缺血发作、心绞痛发作、急性心肌梗死、心脏骤停或猝死、急性心力衰竭、严重的心律失常（需要住院或持续超过24 h）及外周血管疾病，均严格参照相应的临床诊断标准[14]。随访时间为2年。随访终点为死亡和心血管事件。随访期间记录所发生的心血管事件及死亡原因，肾移植患者或转为腹膜透析者记为删失。院外死亡患者通过电话访问家属以了解可能的死亡原因。患者发生多起心血管事件时，以第一次事件的时间作生存分析。

1.4 统计分析

统计分析采用SPSS16.0软件。计数资料采用频数和百分比表示，组间差异采用χ^2检验；计量资料采用均数标准差或中位数及四分位数表示，组间差异采用t检验（变量呈正态分布）或Mann-Whitney U检验（变量呈非正态分布）。采用Kaplan-Meier生存曲线及Cox回归分析患者的全因死亡、心血管死亡及新发心血管事件的影响危险。P<0.05认为差异有统计学意义。

2 结果

2.1 基线资料

302例MHD患者中，男性为162例（占53.6%），初始透析的平均年龄为58.2岁，入组前透析时长中位数为23.1个月。基础病主要为慢性肾小球肾炎（29.8%）、糖尿病肾病（25.5%）、高血压肾病（26.8%）和梗阻性肾病（8.6%）。99例心脏瓣膜钙化患者中，58例为二尖瓣钙化，17例为主动脉瓣钙化，24例同时伴有二尖瓣及主动脉瓣钙化。HVC与无HVC组患者的基线资料具有可比性，但与无HVC组相比，伴有HJVC的患者，初始透析年龄更大，进入维持透析的时间更长，伴有中重度瓣膜返流的患者比例更多，且血钙、血磷及C反应蛋白水平更高（P<0.05，表1、2）。

表1 伴或不伴心脏瓣膜钙化的维持性血液透析患者的一般资料

Tab.1 Baseline demographic and clinical characteristics of MHD patients with or without HVC

Characteristics	HVC (n=99)	Non-HVC (n=203)	P
Age at HD onset (year)	60.9±12.9	55.9±15.8	0.021
Gender (M/F)	52/47	110/93	0.786
Duration of HD before enrolled (month, range)	41.6 (18.6-73.6)	17.0 (7.5-43.5)	<0.001
Pre-HD SBP (mmHg, *Mean*±*SD*)	152±36	148±23	0.154
Pre-HD DBP (mmHg, *Mean*±*SD*)	75±18	76±16	0.740
Body mass index (kg/m^2, *Mean*±*SD*)	21.1±3.0	21.4±3.0	0.578
Smokers (n, %)	14 (14.1)	27 (13.3)	0.841
Diabetes (n, %)	40 (40.4)	62 (30.5)	0.089
Hypertension (n, %)	89 (89.9)	190 (93.6)	0.256
History of CVE before enrolled (n, %)	32 (32.3)	59 (29.1)	0.562
Valvular disease (moderate-to-severe, n, %)	37 (37.4)	49 (24.1)	0.017
Systolic dysfunction (n, %)	9 (9.1)	26 (12.8)	0.344
Diastolic dysfunction (n, %)	53 (53.5)	93 (45.8)	0.207
LV hypertrophy (n, %)	12 (12.1)	7 (3.4)	0.004
LV dilation (n, %)	36 (36.4)	75 (36.9)	0.922
LVEF (%, *Mean*±*SD*)	64.7±11.4	62.4±10.9	0.098
Ultrafiltration rate (mL/kg/h, *Mean*±*SD*)	11.1±4.4	11.0±4.7	0.793
Medications (n,%)			
Calcium channel blockers	70 (70.7)	131 (64.5)	0.286
ACEI/ARB	47 (47.5)	96 (47.3)	0.976
ACEI+ARB	5 (5.1)	19 (9.4)	0.194
Beta blockers	54 (54.5)	108 (54.2)	0.826
Alpha blockers	46 (46.5)	71 (35.0)	0.054

HVC: Heart valuvlar calcification; CVE: Cardiovascular events; LVEF: Left ventricular eject fraction; AVF: Arterial-venous fistula.

表2 伴或不伴心脏瓣膜钙化的维持性血液透析患者的实验室资料

Tab.2 Baseline hemodialysis indices and biochemical parameters of patients with or without HVC

Characteristics	HVC (*n*=99)	Non-HVC (*n*=203)	*P*
URR (%, *Mean*±*SD*)	69.8±8.2	70.5±8.6	0.516
Kt/V (*Mean*±*SD*)	1.6±0.3	1.6±0.3	0.519
ALB (g/L, *Mean*±*SD*)	30.8±3.2	30.4±4.2	0.348
Hb (g/L, *Mean*±*SD*)	102.6±21.5	96.2±21.8	0.016
Ferritin (ng/mL, range)	313 (94-714)	271 (89-578)	0.254
TSAT (%, *Mean*±*SD*)	27.8±18.3	28.1±18.0	0.872
Serum calcium (mmol/L, *Mean*±*SD*)	2.5±0.2	2.4±0.2	0.019
PO4 (mmol/L, *Mean*±*SD*)	2.3±1.0	2.0±0.7	0.006
iPTH (pg/mL, range)	256 (79-627)	192 (97-402)	0.109
ALP (U/L, range)	73 (56-111)	65 (51-91)	0.073
β2-microglobin (mg/L, *Mean*±*SD*)	39.2±13.6	38.2±14.6	0.608
CRP (mg/L,range)	6.6 (2.5-12.8)	3.5 (1.6-8.8)	0.003
Uric acid (mmol/L, *Mean*±*SD*)	436±91	430±109	0.622
Cholesterol (mmol/L, *Mean*±*SD*)	4.2±1.1	4.2±1.1	0.859
Triglycerol (mmol/L, *Mean*±*SD*)	1.5±1.2	1.4±1.1	0.306
HDL-cholesterol (mmol/L, *Mean*±*SD*)	1.0±0.3	1.1±0.4	0.137
LDL-cholesterol (mmol/L, *Mean*±*SD*)	2.2±0.8	2.2±0.9	0.467

HVC: Heart valuvlar calcification; Kt/V: Urea clearance index; ALB: Albumin; Hb: Hemoglobin; TSAT:transferrin saturation; iPTH:intact parathyroid hormone; ALP: Alkaline phosphatase; CRP: C-reactive protein; URR: Urea reduction ratio.

2.2 生存情况

随访结束时,有5例患者接受肾移植,无1例患者转腹膜透析或脱失。共63例(20.9%)患者死亡,其中HVC组30例(30.3%),无HVC组33例(16.3%,*P*<0.05)。共36例(11.9%)死于心血管事件(占死亡总数的57.1%),其中HVC组22例(22.2%),无HVC组14例(6.9%,*P*<0.05,表3)。心血管死亡包括8例急性心肌梗死、8例脑卒中,19例猝死和1例外周血管动脉闭塞。其他死亡原因包括11例肺部感染或呼吸衰竭、2例重度营养不良、4例恶性肿瘤,1例肝衰竭及9例未知原因。

表3 伴或不伴心脏瓣膜钙化的血液透析患者的终点事件比较

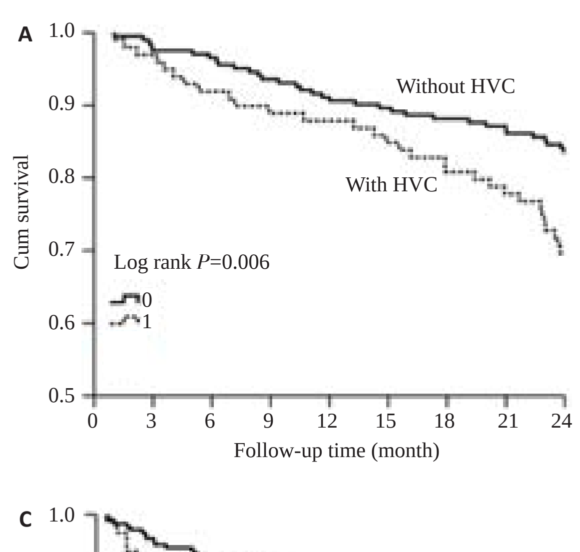
Tab.3 Comparison of all-cause mortality, cardiovascular mortality and cardiovascular events between HVC and non-HVC patients

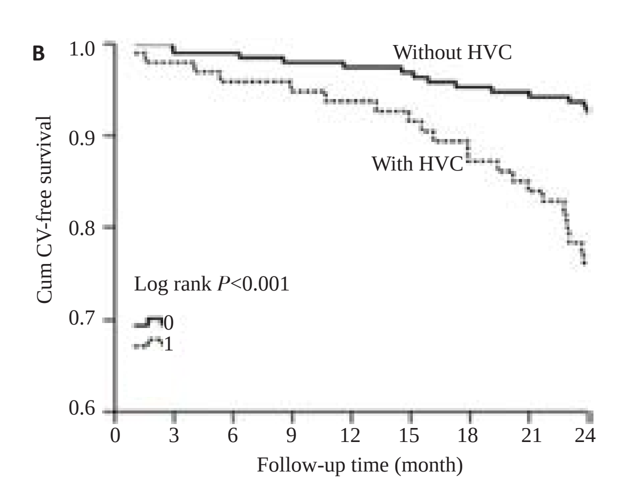
	All (*n*=302)	HVC (*n*=99)	Non-HVC (*n*=203)	*P*
All-cause mortality	63 (20.9)	30 (30.3)	33 (16.3)	0.005
CV mortality	36 (11.9)	22 (22.2)	14 (6.9)	<0.001
New onset CV events	100 (33.1)	48 (48.5)	52 (25.6)	<0.001
Angina pectoris or AMI	28 (9.3)	15 (15.2)	13 (6.4)	0.014
Cardiac arrest	18 (6.0)	12 (12.1)	6 (3.0)	0.002
Acute heart failure	33 (10.9)	22 (22.2)	11 (5.4)	0.943
Arrhythmia for hospitalization	22 (7.3)	11 (11.1)	11 (5.4)	0.074
Stroke	23 (7.6)	13 (13.1)	10 (4.9)	0.012
Transient ischemia attack	5 (1.7)	2 (2.0)	3 (1.5)	0.664
Peripheral vascular disease	3 (1.0)	1 (1.0)	2 (1.0)	1.000

CV: Cardiovascular; HVC: Heart valuvlar calcification. AMI: Acute myocardial infarction.

2.3 心脏瓣膜钙化可预测全因死亡、心血管死亡和新发心血管事件

Kaplan-Meier生存分析曲线见图1。HVC与增加的全因死亡率(图1A,P=0.006)和心血管死亡率(图1B,P<0.001)相关。经多因素校正后,HVC仍然是预测全因死亡(风险值HR为1.88,95%可信区间CI为1.11-3.19,P=0.019)及心血管死亡(HR为3.47,95%CI为1.76-6.84,P<0.001)的独立危险因素(表4)。





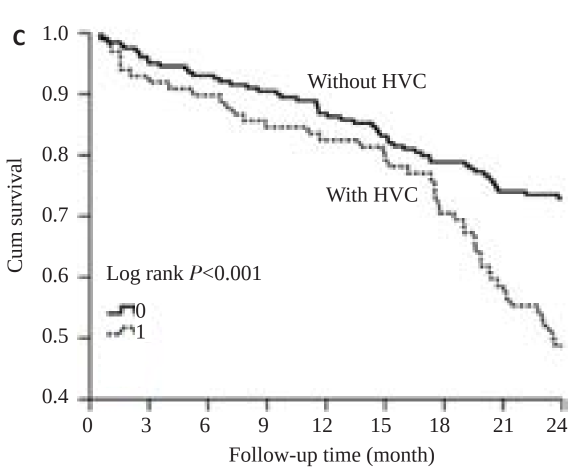


图1 伴或不伴心脏瓣膜钙化的患者生存曲线分析

Fig.1 Kaplan-Meier estimates of all-cause mortality (*A*), cardiovascular mortality (*B*) and incidence of cardiovascular events (*C*) in MHD patients with or without HVC.

同样,HVC与增加的心血管事件相关(图1C,P<0.001)。100例(33.1%)患者有新发心血管事件,HVC组48例(48.5%),无HVC组52例(25.6%),两组间有统计学差异(0.001)。新发心血管事件中,最常见的事件为急性心衰发作(占新发心血管事件的33%),其次为脑卒中(23%)和猝死(18%)。HVC组与无HVC组在急性冠脉事件、心脏骤停及卒中事件方面,存在统计学差异(P<0.05,表3)。经多因素校正后,HVC仍然是预测新发心血管事件的危险因素(HR为1.64,95% CI为1.09-2.47,P=0.017,表4)。

3 讨论

心脏瓣膜钙化(HVC)对透析患者全因预后的影响已经明确,其在腹膜透析和血液透析患者均明显增加死亡风险[5,9]。基于既往的这些证据,KDIGO指南建议,血管或心脏瓣膜的筛查有助于对透析患者进行危险分层,且心脏超声是简单方便且无创的发现HVC的检查手段[8]。我们的研究结果显示,HVC不仅增加全因死亡和心血管死亡风险,而且明显增加MHD患者新发心血管事件风险,这不仅支持KDIGO指南的推荐,也提供了更新的证据,即HVC与心血管预后密切相关。

目前关于HVC与MHD患者心血管预后的证据并不多。Wang最早报道了HVC对192例长期腹膜透析患者(62例伴有HVC)的心血管死亡影响[5]。随访17.9个月后,HVC组与非HVC组心血管死亡率分别为22%和3%;HVC的心血管死亡风险是非HVC组患者的5.39倍。日本一项包含1290例新进入血液透析治疗的患者的队列研究,观察了心脏超声评估的HVC对心血管死亡的影响。结果发现,随访中位数51个月后,HVC组25.9%患者死亡,12.1%死于心血管疾病,HVC组全因死亡和心血管死亡率均高于非HVC组[11]。另一项研究在患者新进入血液透析(212例)或腹膜透析(44例)时进行了HVC的评估。50%的患者伴有HVC。随访42.1±30.2月之后发现,26.6%患者发生终点事件(心梗、卒中

表4 Cox回归分析影响全因死亡、心血管死亡及新发心血管事件的因素

Tab.4 Multivariate Cox regression model of factors predicting all-cause or cardiovascular mortality and cardiovascular events

Covariate	Unadjusted		Adjusted	
	Hakard ratio (95% CI)	*P*	Hakard ratio (95% CI)	*P*
All-cause mortality*				
Age at HD onset (per 1 year)	1.05 (1.03-1.07)	<0.001	1.04 (1.01-1.06)	0.002
CRP (per 1mg/L)	1.02 (1.01-1.03)	0.001	1.02 (1.01-1.03)	0.006
Beta-blocker	0.50 (0.31-0.83)	0.008	0.50 (0.29-0.88)	0.016
History of CV events	2.15 (1.31-3.53)	0.002	1.90 (1.10-3.28)	0.021
HVC	1.98 (1.21-3.24)	0.007	1.88 (1.11-3.19)	0.019
Cardiovascular mortality†				
LV systolic dysfunction	2.94 (1.38-6.25)	0.005	3.25 (1.52-6.97)	0.002
History of CV events	3.57 (1.84-6.92)	<0.001	3.79 (1.92-7.47)	<0.001
HVC	3.45 (1.76-6.74)	<0.001	3.47 (1.76-6.84)	<0.001
Cardiovascular events‡				
Age at HD onset (per 1 year)	1.05 (1.03-1.07)	<0.001	1.05 (1.03-1.07)	<0.001
Gender (male yes)	1.61 (1.08-2.41)	0.021	1.66 (1.07-2.59)	0.024
CRP (per 1mg/L)	1.02 (1.00-1.03)	0.005	1.02 (1.01-1.03)	0.002
ACEI or ARB	1.64 (1.10-2.44)	0.015	1.76 (1.14-2.72)	0.011
History of CV events	2.43 (1.64-3.60)	0.000	1.64 (1.08-2.49)	0.020
HVC	2.08 (1.40-3.08)	<0.001	1.64 (1.09-2.47)	0.017

*Adjusted for age at HD onset, diabetes, beta-blocker, ACEI or ARB, pre-HD DBP, serum phosphorus, serum albumin, CRP, uric acid, LV systolic dysfunction, history of CV events and HVC. †Adjusted for age at HD onset, duration of HD, moderate-to-severe valvular diasease, pre-HD DBP, LV systolic dysfunction, history of CV events and HVC. ‡adjusted by gender, age at HD onset, medication with ACEI or ARB, URR, Kt/V, CRP, moderate-to-severe valvular diasease, history of CV events and HVC. LV: left ventriulcar; HVC: heart valuvlar calcification.

事件或心血管死亡)。伴有HVC者发生终点事件的风险为无HVC者的几乎2倍[12]。相比之下,本研究的观察对象是进入维持性血液透析治疗的患者,随访2年后,HVC组30.3%患者死亡,22.2%死于心血管疾病。与非HVC相比,HVC的心血管死亡风险是非HVC组的3.87倍。国内一项研究也显示,伴HVC的MHD患者死亡率为51.6%,心血管死亡率为25.8%[10]。因此,无论是腹膜透析还是血液透析的替代治疗手段,无论是刚刚启动血透治疗的患者,还是进入维持血透的患者,HVC均明显增加全因死亡和心血管死亡风险。此外,上述日本的研究中还发现,同时伴有两个瓣膜(主动脉瓣和二尖瓣)钙化的患者比只伴一个瓣膜钙化的患者预后差。主动脉瓣和二尖瓣膜均钙化的患者,其心血管死亡风险是无瓣膜钙化者的2.8倍[11]。但是本研究并未观察到多个瓣膜钙化比单个瓣膜钙化的结局更差,可能与分成亚组后样本量小有关。

本研究的重要性在于进一步探讨了HVC对MHD患者新发心血管事件方面的影响。随访结束时,HVC组中接近半数患者发生新的心血管事件,而非HVC组只有1/4发生。在具体的心血管事件中,两组在急性冠脉事件、心脏骤停及卒中方面有显著差异,提示HVC与动脉粥样硬化密切相关。早在20世纪60~70年代,解剖学证据即表明HVC与冠脉钙化存在一定的关联[15-16],提示HVC是动脉粥样硬化的一个标志物[17-19]。影像学证据也表明,心脏彩色多普勒手段检测的HVC与CT扫描所获得的冠脉钙化和/或主动脉钙化病变较为吻合[20],即HVC一定程度上可同步反映冠脉钙化情况。此外,也有研究发现,冠脉钙化和HVC在伴有缺血性心脏病的ESRD患者中较为普遍及严重[21-23]。这些可以解释HVC与急性冠脉事件的相关性。关于HVC与心脏骤停,也有研究表明,过高的心脏钙负荷增加猝死的几率[24-25]。目前关于透析患者脑血管钙化的研究非常少,未见关于HVC增加卒中事件的报道。

本研究还观察到,初始透析年龄、透析时长、左室肥厚、中重度瓣膜返流、血红蛋白、血钙、血磷及C反应蛋白相关,这与既往的报道较为一致[26],表明MHD血管钙化可能是多因素作用后的结果。其中,微炎症状态可能是同时导致血管或瓣膜钙化及动脉粥样硬化的重要原

因。在Cox回归分析中,我们发现,C反应蛋白也是影响全因死亡和新发心血管事件的独立危险因素。还有学者观察到,C反应蛋白联合心脏瓣膜钙化可进一步提示ESRD患者预后不良[27-28]。

综上,本研究探讨了HVC对MHD患者心血管预后的影响,结果显示,HVC是MHD患者心血管死亡、新发心血管事件的独立危险因素。心脏超声作为合理的替代CT扫描(金标准)的检查手段,有助于在血液透析人群筛查心血管高危患者。

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